An experience on pediatric burn wounds treated with a plant-derived wound therapeutic

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Objective: To evaluate the efficacy of a plant-derived wound dressing, a mixture of hypericum oil (*Hypericum perforatum*) and neem oil (*Azadirachta indica*), in different types of pediatric burn wounds.
Method: A retrospective review was conducted on pediatric patients presenting with second degree burns, partial or total failure of skin graft performed with domestic conventional protocol or ulceration of keloid scar of previous burn under treatment with a plant-derived wound dressings (1 Primary Wound Dressing; Phytoceuticals AG), from June to August 2012. Time to healing, wound size, ease of handling, pain and complications were evaluated.
Results: 9 paediatric patients (older than five years: mean age 9,6±2,39, 8-14 years) presenting with mixed simple and partial/full-thickness second degree burns were analysed for procedural and background pain during the first week of treatment after trauma. Patients reported a strong relief of procedural and background pain from an initial value of 7-8/10 to 0/10 within the first week of treatment. Pain relief of the procedural and background pain was recorded on 6 out of 9 patients (older than five years) at the second and third week of treatment. Nine patients (mean age 8.17±3.35; (1-11 years) were analysed retrospectively over the whole healing course. Mean wound size was 50,76±48,32 cm^2 (4,63-132 cm^2). A rapid induction of granulation tissue was observed. The time to complete healing by secondary intention was 16,6±4,69 days (10-22 days). No infective complications were recorded
Conclusion: This retrospective, non-controlled analysis suggests that ONE is very simple to use, safe and potentially effective therapy for the treatment of burn wounds, it is effective on reducing procedural and background pain from the first days after trauma.
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Introduction

Burns are the second cause of child accidents in Bolivia mainly due to poverty. Statistically, most frequent burns are provoked by hot water, especially in small children under five, principally for lack of supervision by parents. Although this situation is very common in other parts of the world (Burd and Yuen 2005, Tse et al, 2006, Kim et al. 2011), in Bolivia the problem is actually very common. In poor families children are usually left unguarded in the only space that serves as kitchen, bedroom, bathroom and living room, where all sorts of dangerous objects can be found (hot water, free flames, gasoline, electric shock, etc). The yearly worrying increase in burns in children makes it mandatory to improve their living conditions especially for those children with extensive and disfiguring scars. Burns, if not properly treated, can lead to several complications (Palmieri and Greenhalgh 2002, Kim et al. 2011) including death (lethal infections) marked functional limitations or malfunction especially in those children with poor living conditions (malnutrition, diarrhea, respiratory problems, etc.).
In Viedma Hospital the assessment of the degree of burn is clinically determined during the first visit by an experienced burn surgeon and it is monitored and re-examined during the following days/weeks in order to both re-assess the burn depth and to apply the best treatment and therapy for each patient, as indicated in many studies (Palmieri and Greenhalgh 2002, National Burn Care Review Committee, UK, 2006, Kim et al.

2011) especially when dedicated instruments such as Laser Doppler Imaging (LDI) (Pape et al. 2001, Monstrey et al. 2008, Jeffery 2009) are not available (Kim et al. 2011).

The treatment of first and partial second degree burns lasts from one week to 10 days as is indicated in many studies (Palmieri and Greenhalgh 2002, Papini 2004, Singer and Dagum 2008, Jaffery 2009). In these cases the domestic protocol is application of hydrogel (Biopiel, Mediderm) containing Chitosan and Polyaminopropyl Biguanide as primary wound dressing without any secondary wound dressing. In case of full-thickness second and third degree burns, which heal in three weeks to 30 days or more in case of complications (Palmieri and Greenhalgh 2002, Papini 2004, Singer and Dagum 2008, Jaffery 2009), escarectomy under sedation in the Operating Theatre is performed immediately and after first and second week after trauma if needed, then cleansing of the wound surface with saline solution is performed daily and local silver sulfadiazine cream (SSD) mixed with lidocaine (Quemacuran-L, INTI, Lima, Perù) as primary wound dressing is applied twice a day; at the second week after trauma, based on the re-assessment of the wound surface residual area, the burn surgeon decides whether to continue the dressing therapy for secondary intention healing or perform an homologous skin graft. This because it is well reported that the risk to develop Keloid reaction and/or hypertrophic burn scar is strictly related to the lengh of the healing time (more than three weeks) (Deitch et al. 1983) and it is higher among Afro-descendants, Asian, Hispanics and other ethnicities having dark skin pigmentation (as we have in Bolivia) as well as among populations having a particular genetic susceptibility (Al-Attar et al. 2006, Butler et al. 2008,Wu et al. 2012,).

Systemic antibiotics are routinely administered to the patients for almost five to seven days, prolonged if infective complications come up. Patients with less severe burns (first and partial second degree burns) are admitted to the hospital for one week and should be examined as outpatients for the complete healing the following week. Most of these patients go missing because they do not come back for the check-up visit. The patients with more severe burns (full-thickness second and third degree burns) are admitted to the hospital as inpatients until a successful skin graft is performed. They need to follow a long term rehabilitation and physiotherapy treatment during which those patients who develop a keloid reaction, have to wear a special compression secondary dressing (Deitch et al. 1983). Very often the patients do not follow the scheduled protocol and come back to hospital only when disfiguring keloid are undergoing ulcerations and/or severe functional limitations which needed to be treated for secondary intention healing or need to be removed by surgery (Butler et al. 2008). If the surgeon decides to heal by secondary intention, the patients are considered as outpatients and they visit the hospital weekly.

Our aim is to shorten the period to healing, alleviate the patient's pain in the acute events and minimize the complications of the burn trauma (infections, failure of grafting, functional limitations, development of exuberant keloid reaction, etc). The ideal burn wound dressing should prevent contamination and desiccation, remove exudate, discourage growth of pathogens and promote wound healing while being both comfortable to apply and remove, easy to use, economical and with a long shelf life (Singer and Dagun 2008). There is clear evidence that antimicrobials (povidone iodine, silver sulphadiazina, chlorhexidine), besides provoking pain, have cytotoxic effects, which impair or delay the healing process (Fraser et al, 2004). At the end an ideal dressing must not provoke pain or should determine pain relief of the procedural pain (pain provoked by medical procedure) and of the background pain (pain properly related to the burn injury) (Abdi and Zhou 2002, Chan et al 2007). The plethora of dressings currently available confirms that such dressings do not yet exist (Singer and Dagun 2008, Kim et al. 2011) and painful cytotoxic antimicrobials are commonly used in conventional management of burns including paediatric patients (Papini 2004, Jefferey 2009, Kim et al. 2011, Rosanova et al. 2012). Recently, a new plant-derived wound therapeutic was introduced to the Swiss market (1 Primary Wound Dressing® [ONE]; Phytoceuticals AG, Zurich, Switzerland). It consists of a mixture of hypericum oil (*Hypericum perforatum*) and neem oil (*Azadirachta indica*), designed to create a moist wound healing environment, with the oil layer preventing the secondary dressing from adhering to the wound. Results from extensive case studies in different types of acute and chronic wounds suggest that ONE can be used as an effective primary wound dressing that promotes wound healing and protects the periwound skin (Hunziker et al. 2012). ONE leads to an impressive induction of granulation tissue, even in very deep wounds (Lauchli 2012). It proved to be simple to use and increases patient comfort greatly (Lauchli et al. 2012). Furthermore, it is thought to have an antimicrobial effect without provoking pain and promotes the regeneration of the epidermis (Desbois and Smith 2010, Lauchli et al. 2012). Because the composition of this plant-derived wound dressing is similar to the normal

constituents of tissue (Free saturated and unsaturated Fatty Acids) it would be expected not to be irritating and sensitising which is a potential problem with the use of topical applied exogenous materials (Drake et al. 2007, Lauchli 2012). Due to the simple mode of application (spray) and the broad mode of action, it could be indicated for the treatment of burns, with the intention of finding an effective alternative to the existing treatment options which rely on the use of local antibiotic ointment and painful cytotoxic disinfectant/antimicrobials.
In this retrospective, non-controlled analysis we evaluated the efficacy of this product on mixed partial and full-thickness second degree burns left to heal under secondary intention, failures of skin graft of burns treated under the aforementioned domestic protocol and ulcerations of healed previous burns which had developed a keloid reaction. An assessment of pain relief was carried out only on patients older than five.

Materials and Methods

A retrospective review was performed on 9 patients admitted at Viedma Hospital, Cochabamba, Bolivia from June to August 2012, which carried a total of 18 wounds: 9 second degree burns (mixed partial and full-thickness in the same patient), 1 partial second degree burn, 2 keloid ulceration, and 6 partial failure of skin graft, all but one left to heal under secondary intention. One case underwent skin graft at day 13 after trauma. The protocol applied consisted of replacing the wound primary dressing of the aforementioned conventional local protocol with the product ONE. Wound area, pain relief and time to healing were recorded. Pain relief was documented during the initial week from trauma on 9 patients older than five but because of the high rate of patients going missing, the pain relief of the next two weeks was recorded only on 6 patients.

Outcomes
Treatment was continued until complete epithelialisation, in the cases that underwent grafting the treatment was continued until the skin graft was assessed as having been successful (the following week).
Wound healing was defined as complete closure by secondary epithelialisation (complete secondary intention healing).
The treatment period was defined as the time between first application of the wound dressing and complete wound closure or graft attachment.
Patients were seen at least every week by a wound-care specialist. Before starting treatment, and at every clinical visit, the wounds were photographed together with a ruler and the wound size as well as the wound area was determined from the photographs using measuring software (Autocad). At each follow-up visit, pain (assessed by open-ended questions, related to the age of the paediatric patients, older than five years), clinical signs of infections, as well as any side effects, were recorded.

Results

9 out of the initial recruited patients were older than five (mean age 9,6±2,39 years: 8-14 years) and could be questioned about pain sensation and pain relief during and after medication. All of them reported that the initial pain of 7-8/10 value decreased to 0/10 value on the visual scale adopted (increasing from 0 to 10) after three-five days of treatment when ONE was used. All patients older than five followed until complete epithelialisation (6 patients: 8-11 years) continued to report no pain during the second and third week of treatment. Nine patients out of the initial group recruited completed the study period. Data and cases are summarized in Table 1 for burns and Table 2 for ulcerations of old keloids. The mean age of the these patients was 8,17+3,35 (1-11 years) and had a total of 18 wounds. The mean size of the mixed simple and full-thickness second degree burns was 50,76±48,32 cm^2 (4,63-132 cm^2). In all cases the Total Body Surface Area (TBSA) was less than 10%. The mean size of the keloid ulcerations was 1.79 cm^2 in one case and similar but not measured in the other case (Table 2).

Table 1. Case reports of patients treated with ONE: Burns

Patient n°	Sex	Age (years)	Burn degree	Healing	Wound size (cm^2)	Time to healing (days)	Latency (days)	TBSA (%)
1	F	11	Mixed II°	S.I.H.	57,19	13	1	4
2	M	3	Mixed II°	P.F.G.	36,91	21	4	5
3	F	8	Mixed II°	S.I.H.	69,18*	14	10	8
4	M	1	Mixed II°	I° G	14,93	21	7	6
5	M	2	Mixed II°	S.I.H.	132,04	18	1	8
6	M	11	MIxed II°	P.F.G.	11,64*	20	17	<3
7	M	11	Simple II°	S.I.H.	4,63	10	1	<1

M= Male F= Female
S.I.H.= secondary intention healing
P.F.G.= (secondary intention after) partial failure of graft
I° G= graft at 13 days
***= data is intended as the sum of the areas of wounds on different anatomic sites**

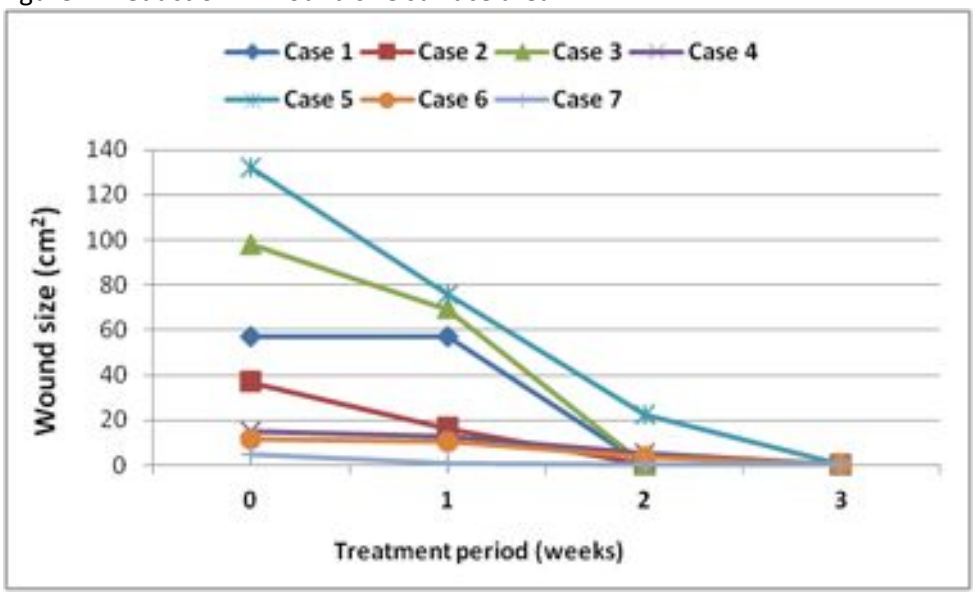
Table 2. Case reports of patients treated with ONE: ulcerations of old keloids

Patient n°	Sex	Age (years)	Type of wounds	Healing	Wound size (cm^2)	Time to healing (days)	Latency (days)
1	M	10	keloid	S.I.H.	1,79	22	3
2	M	6	keloid	S.I.H.	ND	11	3

S.I.H.= secondary intention healing

14 out of 15 wounds (8 cases) healed by secondary intention without any further surgical or other intervention (Case n°2 and Case n° 6- were partial failure of skin graft, Table 1), one underwent a successful skin graft at 13 days after trauma (Case n° 4). The mean days of time to healing for all the wounds considered was 16,6±4,69 days (10-22 days) (See Table 1 and 2). In Figure 1 treatment period (weeks) and reduction of wound surface area for mixed simple/full-thickness second degree burns (7 cases) are reported.

Figure 1. Reduction in wound size surface area



No wound exhibited clinical evidence of superficial or deep infection. None of the patients showed signs of allergic reaction and no other side effects were observed. Review of clinical photographs of the healed wounds showed a cosmetically satisfying outcome in all patients.

Discussion

One of the most important aims in curing paediatric burn patients is to alleviate the patient's pain as much as possible. The pain experienced from the wound care procedure is known as procedural pain and occurs during and after wound care, while background pain refers to the burn pain experienced by the patients when at rest (Abdi and Zhou 2002, Chan et al 2007, Burns Management Guidelines, Melbourne Australia 2012). The burn pain and wound care procedures often increase the patients' anxieties, which exacerbates their perception of pain (Chapman 1985) especially when the sufferers are children who, due to their fear of painful procedures, typically experience a high level of anxiety before and during wound care treatment for burns (Mcclam, 2000).

Because the aforementioned domestic protocol does not include the use of bandaging, which is strongly painful if the secondary dressing sticks to the wound surface, in this retrospective not controlled study the procedural pain was limited to the cleansing of the wound surface using saline solution and renewal of medication based on daily application of ONE. We observed that the application of ONE never provoked pain (procedural pain) and the paediatric patients did not became stressed during the wound care procedure but became confident with the spray procedure and demanded to be sprayed because of the strong background pain relief obtained after the application. The pain relief experienced by the paediatric patients was also reported by the parents of the outpatients following the scheduled dressing protocol at home. The requests to be sprayed were more frequent during the first week after trauma (inflammatory phase) than in the following period in which no other applications over the daily wound care procedure were scheduled. The inflammatory phase is a major factor in the presence of background pain because the high level of metabolic activities at the burnt area, the high level of oxygen free radicals, of different types of catabolites deriving from the injured tissue, of chemical mediators and inflammatory cells acting to limit and repair the damaged tissues (Pederson 1998, Latha and Babu, 2001). Burn pain is related also to the stimulation by the air of the ends of the sensitive fibres of the damaged nerves left uncovered by the trauma. Some folk remedies in which different sources of oil or grease are included, typically are applied to impede the contact of the air on damaged surface, especially in the case of painful depths of burns (second degree) (Cuttle et al. 2009). Modern burn treatments include several occlusive dressings in order to obtain pain relief and protection of the damaged area, but because of high volumes of exudate during the inflammatory phase and the risk of infection under occlusive dressings, it is not always possible to

completely isolate the burn surface from contact with the air (Latha and Babu, 2001, Jeffery 2009, Cleland 2012) to obtain complete pain relief. Indeed, secondary intention healing is commonly considered painful, with a high infection rate, demanding extensive care and resulting in inferior cosmetic outcomes. Our case series shows that secondary intention healing is not associated with infection or pain. ONE acts by forming an oily protective layer (mechanical isolation) on the damaged surface, which may probably be responsible for the pain relief reported in this case series during the most painful period (first and second week after trauma). The high volumes of exudate from the wound surface during this first phase of the healing process cause the superficial oily layers created by the dressing to break up more rapidly , so that they need to be re-applied more than once a day to re-establish the protective and pain-relief mechanical barrier.

The healing period observed on the 9 cases followed till complete epithelialisation (see table 1) was similar to the expected period of second degree burns in which antimicrobials/disinfectant are used (from 15 to 21 days) (Palmieri and Greenhalgh 2002, Kim et al. 2011). We obtained this result without ever using antimicrobials/disinfectant and without having complications from infection. The induction of granulation tissue formation was impressive, resulting in progressive filling up of the wound surface and in re-epithelialisation. This effect may be explained by the antimicrobial activity of the fatty acids contained in the spray (Desbois et Smith, 2010) and the balanced moist environment obtained by the semi-occlusive layer the oil creates (Sharman, 2003)

The low number of cases treated in this study does not allow a statistical calculation of the incidence of infections. These results confirm what has been reported in other studies in which no infective complications were observed using ONE without using antimicrobials (Laeuchli 2012, Laeuchli et al. 2012). The possibility to avoid the use of painful cytotoxic agents without exposing the injured tissue to infection, open a new way for comfortably and presumably correctly managing burn injuries, especially in paediatric patients.

The literature reports that the risk off developing keloid in susceptible populations is also related to the length of time to healing exceeding three weeks (Deitch et al. 1983). The time to healing of less than three weeks from trauma observed in this case series may be in favour of diminishing the incidence of keloid complications. Because some of the patients did not come to the hospital for follow up control, it was not possible to verify the incidence of keloid reaction in the patients treated. It will need more studies to verify whether patients, having a high risk of developing Keloid, as the Bolivian people have, could show differences in developing keloid reactions after having been treated with ONE.

Skin grafting and surgical options result in considerable costs. The present retrospective non-controlled analysis suggests that ONE is a promising therapy to support the healing process by both reducing the use of skin graft and recovering the partial failure of the skin graft performed without the relative costs of other hospitalisations of the patients. Even though with ONE a daily dressing change is required, the outpatients only visit the hospital once a week for a clinical control. The treatments between visits can be performed by the patient, the patient's relatives or a home care organisation, as the dressing change procedure is very simple, rapid and not painful. This examples suggest that use of ONE could offer economic advantages over alternative treatments; nevertheless a specific study on the comparative cost effectiveness of treatments will be required.

Limitations

There are a number of limitations of this study. The study included only a small number of patients, recruited from a single centre, with data analysed retrospectively. This makes interpretation of the results challenging; indirect comparison with published data on the management of such wounds has to be undertaken carefully, even if the characteristics of the wounds included in this study, and their prognostic indicators, are similar to those reported in other published trials. Despite this, the results seemingly compare favourably with those from the literature.

Conclusion

The results of this retrospective non-controlled analysis suggest that the plant-derived wound spray is clinically efficacious for burnt soft tissue. Further studies, with a larger population, are required to document the effectiveness of this wound spray in a controlled fashion.

Bibliography

1) Abdi S & Zhou Y. Management of pain after burn injury. Current Opinion in Anaesthesiology. 2002, 15: 563–567;
2) Al-Attar A, Mess S, Thomassen JM, Kauffman CL, et al. Keloid pathogenesis and treatment. Plast. Reconstr. Surg. 2006,117: 286-300;
3) Burd A. and Yuen C. A global study of hospitalized paediatric burn patients. Burns 2005, 31: 432–438;
4) Burns Management Guidelines, The royal Children's Hospital, Melbourne and Victorian Adult Burns Service, . web site: www.vicburns.org.au - last updated 30/04/2012;
5) Butler PD, Longaker MT and Yang GP. Current progress in keloid research and treatment. J. Am. Coll. Surg. 2008, 206: 731-741;
6) Chan E.A., Chung J.W.Y., Wong T.K.S., Lien A.S.Y. and Yung Yang J. Application of ea virtual reality prototype for pain relief of pediatric burn in Taiwan. J. Clin. Nurs., 2007, 16: 786-793;
7) Chapman C. Psychological factors in postoperative pain and their treatment. In Acute Pain (Smith G & Covino BG eds), Butterworths, London, 1985, pp. 22–41.
8) Cleland H. Thermal burns. Australian Family Physician. 2012, 4:372-375;
9) Deitch E.A., Wheelahan T.M., Paige-Rose M., Clothier J and Cotter J. Hypertrophic burn scars: Analysis of variables. J. of Trauma. 1983, 23(10):895-898;
10) Desbois A. P. and Smith V. J. Antibacterial free fatty acids: activities, mechanisms of action and biotechnological potential. Appl. Microbiol. Biotechnol. 2010, 85:1629–1642;
11) Drake D.R., Brogden K.A., Dawson D. V and Wertz P.W. Antimicrobial lipids at the skin surface. J. Lipid Res. 2008, 49: 4-11;
12) Fraser J F, Cuttle L, Kempf M and Kimble R M. Cytotoxicity of topical antimicrobial agents used in burn wounds in Australasia. 2004, ANZ J. Surg. 2004, 74: 139-142;
13) Hunziker T, Hafner M, Streit S, Laeuchli S. Pflanzlicher Wundspray fuer akute und chronische Hautwunden. Wund Management 2012, 06: 270-274
14) Jefferey S.L.A. Current burn wound management. Trauma, 2009, 11:241-248;
15) Kim L K P, Martin H C O and Holland A J A. Medical management of pediatric burn injuries: Best Practice. J. Pediatr. Child Health 2011, 48: 290-295;
16) Latha B. and Babu M. The involment of free radicals in burn injury: a review. Burns, 2001, 27: 309-317;
17) Lauchli S. 1 Primary Wound Dressing®: clinical experience. A novel wound dressing, formulated from natural oils, promotes effective healing, protects periwound skin and leads to an impressive induction of granulation tissue, even in deep wounds. HHE, 2012, 1-3;
18) Lauchli S. Hafner J., Wehrman C., French L.E. and Hunziker T. Post-surgical scalp wounds with exposed bone treated with a plant derived wound therapeutic**.** J. W. C. 2012, 21: 228-233;
19) National Burn Care Review Committee, UK, 2006, http://www.britishburnassociation.org;
20) Mcclam E. (2000, September 14). Gorillas easing patients' pain: the beasts are featured in computer games made to distract youngsters during cancer treatments. Philadelphia Inquirer F3,
21) Monstrey S, Hoeksema H, Verbelen J *et al*. Assessment of burn depth and burn wound healing potential. *Burns* 2008; 34: 761–9;
22) Palmieri T. And Greenhalgh D. Topical treatment of pedatric patients with burns. A pratical guide. Am. J. Clin. Dermatol. 2002, 3(8): 529-534;
23) Pape S.A., Skouras C.A. and Byrne P.O. An Audit of the use of laser Doppler imaging in the assessment of burns of intermediate depth. Burns, 2001, 27:233-239;
24) Papini r. Management of burn injuries of various depths. British Med. J. 2004, 329: 158-160;
25) Pedersen JL, Kehlet H. Hyperalgesia in a human model of acute inflammatory pain: a methodological study. *Pain* 1998; **74**(2-3): 139-51;
26) Rosanova M.T., Stamboulian D. and Lede R. Systematic review: which topical agent is more efficacious in the prevention of infections in burn patients? Arch Argent Pediatr, 2012, 11(04): 298-303;

27) Sharman, D. Moist wound healing: a review of evidence, application and outcomes. Diabetic Foot. 2003, 6: 112–120;

28) Singer A J, and Dagun AB. Current Management of acute cutaneous wounds. N.Engl: J. Med. 2008, 359: 1037-1046;

29) Tse T , Poon C H Y., Tse K-H, Tsui T-K, Ayyappan T and Burd A. Paediatric burn prevention: An epidemiological approach Burns, 2006, 32: 229–234;

30) Wu Y., Wang B., Li Y.H., Xu X.G., Luo Y.J., Chen J.Z.S., Wei H.C., Gao X.H and Chen H.D.. Meta-analysis demonstrates association between Arg72Pro polymorphism in the *P53* gene and susceptibility to keloids in the Chinese population. Genetics and Molecular Research, 2012. 11 (2): 1701-1711.

Figure 1. Case n° 1: Mixed second degree burn: first visit

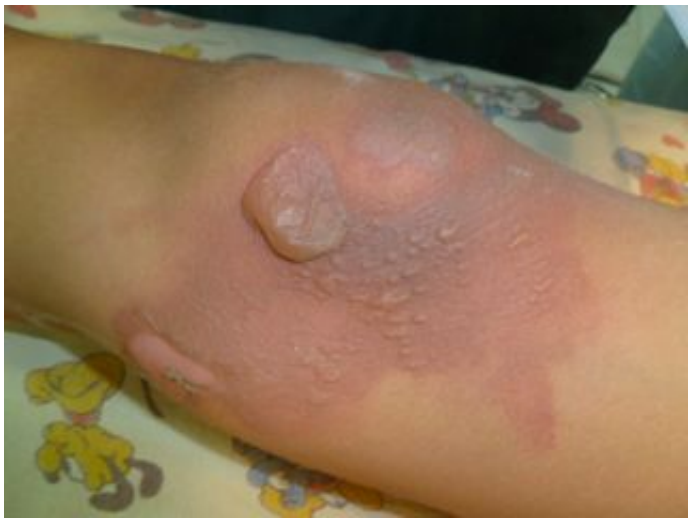


Figure 2. Case n° 1: After surgical debridement (under sedation)

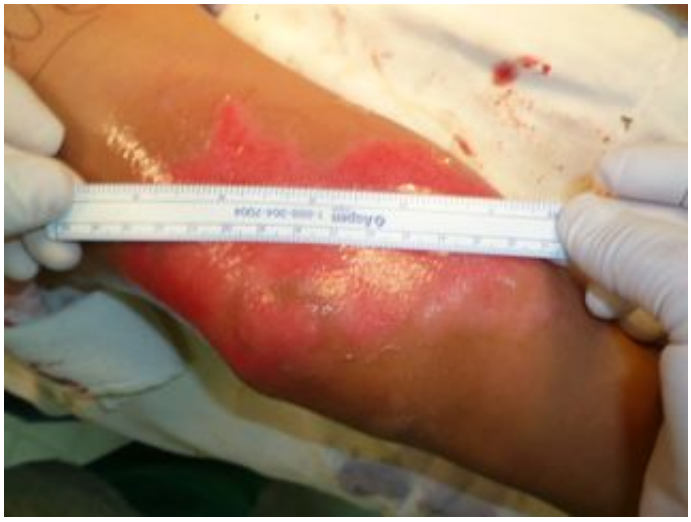


Figure 3. Case n° 1: after one week- riepithelialisation of 25% of the wound surface

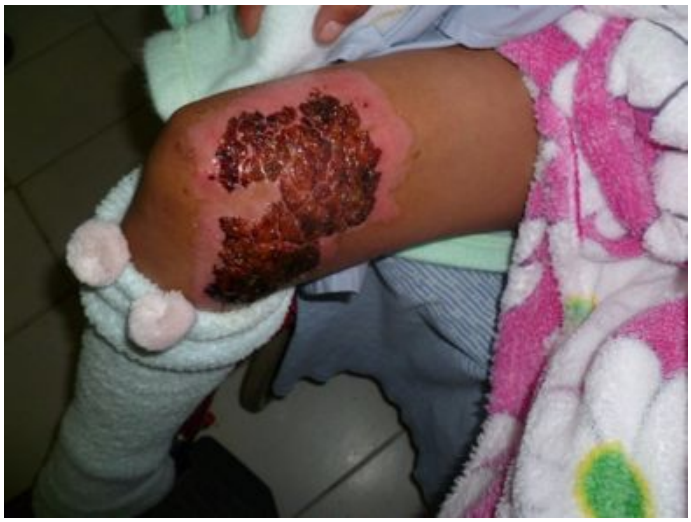


Figure 4. Case n° 1: after two weeks riepithelialisation of 100% of wound surface.

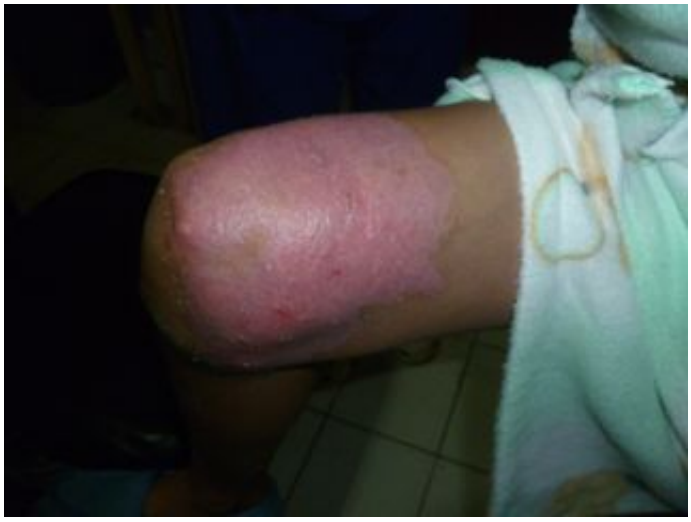


Figure 5. Case n° 8: Partial failure of skin graft, day of surgery debridment under sedation and start of One treatment

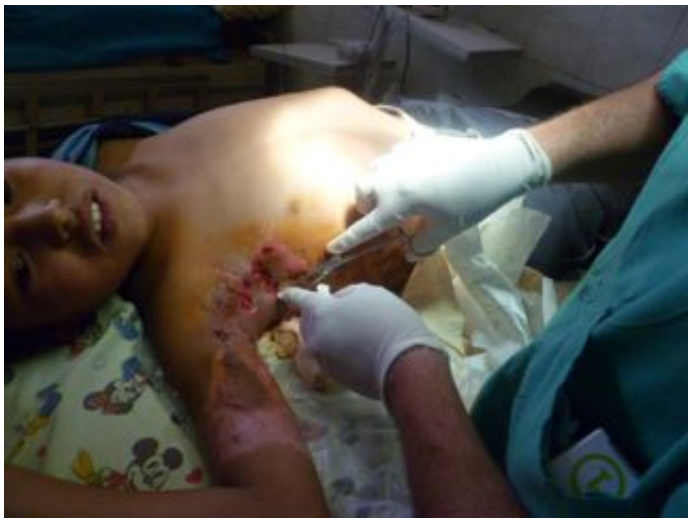


Figure 6. Case n° 8: Partial failure of skin graft, aspect of the wounds after surgery debridment under sedation

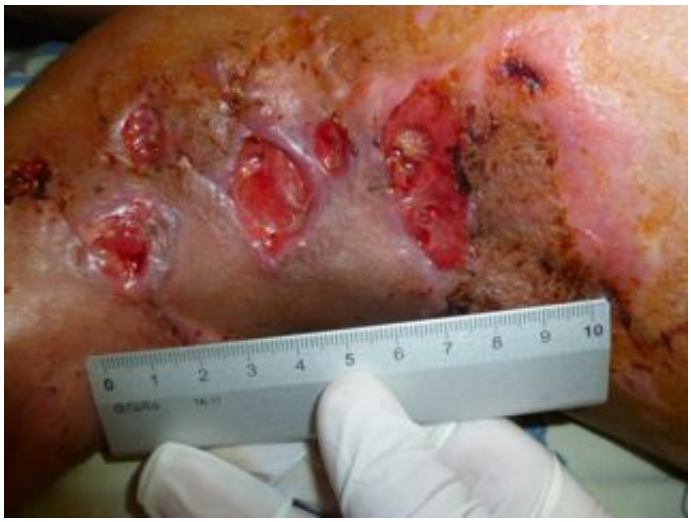


Figure 7. Case n° 8: after one week of ONE Primary Wound Dressing treatment

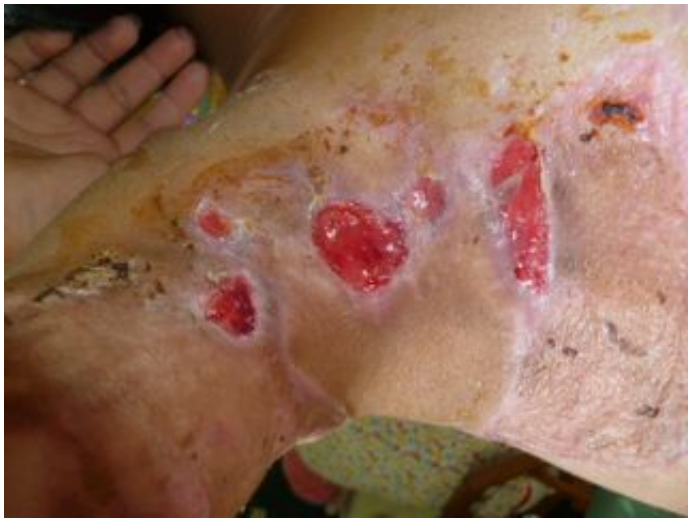


Figure 8. Case n° 8: after two weeks of treatment